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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,462	07/30/2007	**Michael Boll**	58212/K163	9726

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EXAMINER	
OLSON, ERIC	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,462	BOLL ET AL.	
	Examiner	Art Unit	
	ERIC S. OLSON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 24-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,24-39,41-47,49-57 and 59-87* is/are rejected.

7)☒ Claim(s) *40,48 and 58* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *August 23, 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/22/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This application is a national stage application of PCT/EP05/50877, filed March 1, 2005. Claims 1 and 24-87 are pending in this application and examined on the merits herein. Applicant's preliminary amendment submitted August 23, 2006 is acknowledged wherein claims 2-23 are cancelled and new claims 24-87 are introduced.

Claim Objections

Applicant is advised that should claim 83 be found allowable, claim 85 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, the two claims both depend from claim 79 and have the exact same limitations.

Claims 31 and 35 are objected to because of the following informalities: They contain typographical errors, namely the phrases "isobtainable" and "isin" which appear to be intended as the phrases "is obtainable" and "is in," respectively. Appropriate correction is required.

Claim Rejections - 35 USC § 101

Claims 70-78 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-26, 28-33, 36, 37, 44, 54, 64, 74, 75, and 82-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the

claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, the claims recite the broad recitations "MS from 0.35 to 0.5," "molecular weight is from above 600000 to 1500000," and "C_2/C_6 ratio is from 2 to 7," for example, and the claims also recite "preferably from 0.39 smaller than or equal to 0.45, especially from greater than 0.4 to 0.44," "preferably from 620000 to 1200000, more preferably from 700000 to 1000000," and ""Preferably from 2.5 to smaller than or equal to 7, more preferably from 2.5 to 6, even more preferably from 4 to 6," which are the narrower statements of the range/limitation.

Claims 70-78 provide for the use of a pharmaceutical formulation, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 55, 56, and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim claims the method of claim 52 with the further proviso, "further comprising …." followed by an additional ingredient. This phrase is nonsensical, as a method comprises process steps, not physical ingredients.

Therefore it is impossible to determine what the limitation means, rendering the claim indefinite.

Claim 60 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim includes the limitation, "wherein the pharmaceutical formulation is used as a volume replacement." It is unclear whether this limitation adds an additional step, "using the formulation as a volume replacement" to the method of the base claim, or whether it merely specifies an intended use of the product produced in this process. Therefore the claim is indefinite.

Claim 59 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim includes the limitation, "wherein the hydroxyethylstarch is at least one of sterile filtered and heat sterilized." It is unclear whether this limitation adds an additional step of sterile filtration or heat sterilization to the method of the base claim, or whether it merely specifies a product-by-process limitation to be applied to the hydroxyethyl starch used in the method. Therefore the claim is indefinite.

Claim 64 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. This claim refers to the molar ratio of hydroxyethylating agent to starch, but does not make clear whether the molar ratio is per mole of starch molecule or per mole of glucose subunit within the starch. Therefore the claim is indefinite.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43, 51, 61, 81, and 87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition containing certain specific pharmaceutically active ingredients such as physiological saline or ringer lactate, does not reasonably provide enablement for compositions comprising any possible physiologically active ingredient whatsoever. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims;

(6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a therapeutic composition. In order to be enabled for the full scope of the claims, one skilled in the art must be able to obtain and use any solution falling within the claims without undue experimentation.

The state of the prior art: There prior art includes a wide diversity of pharmaceutical substances which can produce a therapeutic effect in the body. Practically every pathological condition known to man can be treated or ameliorated by administration of some sort of substance. However there is no clear commonality between all therapeutic substances that would allow one skilled in the art to clearly predict what compounds are or are not useful as therapeutic substances. Instead, research is ongoing and a vast amount of original, unpredictable research is committed to discovering new pharmaceutically active substances.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The human body is extremely complex, involving many different interconnected physiological systems, any of which can potentially be subject to disease. For each of these systems, there are many different possible targets which could be modified by the administration of a pharmaceutically active substance. Because of this complexity, it is impossible to predict with any degree of certainty what compounds will be effective as pharmaceutically acceptable ingredients.

The Breadth of the claims: The claimed invention is extremely broad, encompassing compositions encompassing all possible pharmaceutically active ingredients.

The amount of direction or guidance presented: The specification describes compositions containing the claimed hydroxyethyl starches as being useful for volume replacement solutions, for increasing blood volume in patients in need thereof. While such a utility clearly supports adding certain pharmaceutically active substances, such as physiological saline, human plasma, or synthetic oxygen carriers, to the claimed compositions, it does not provide any basis for enabling one skilled in the art to practice the invention with the full scope of all possible pharmaceutically active agents.

The presence or absence of working examples: *In vivo* working examples are provided wherein starches according to the instant claims, in combination with 0.9% saline, are infused into animal subjects. These solutions did not contain any additional pharmaceutically active ingredient besides the hydroxyethyl starch and physiological saline.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the discovery of novel therapeutic agents. See MPEP 2164.

The quantity of experimentation necessary: One of ordinary skill in the art, in order to practice the claimed invention with the full range of pharmaceutically active agents beyond the meager number disclosed in the specification would be required to test potential compounds *in vivo* to determine whether a particular compound is useful

as a pharmaceutically active agent. According to the 2006 Chemical Abstracts catalog, (Reference included with PTO-892) The Chemical Abstracts Registry contains entries for approximately 26 million compounds, all of which are potentially included in the claimed invention if they happen to have pharmaceutical activity. For most compounds, it is unknown whether they are or are not useful as pharmaceutically active agents. Gathering this data for every compound known to man would involve *in vitro* screening of an enormous diversity of chemical compounds for pharmaceutical activity, as well as *in vivo* testing of compounds having this activity involving either human or animal subjects to determine therapeutic utility. Because of the unpredictability of the art and the lack of comprehensive working examples covering any significant portion of the total number of potential ingredients, there would be no expectation of success and any positive result would be surprising and unpredictable, thus presenting an a burden of undue experimentation to anyone practicing the invention with the full range of pharmaceutically active ingredients claimed.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for all possible pharmaceutically active ingredients.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 24-34, 42, 43, 52, 60, and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sommermeyer et al. (US patent 7285661, cited in PTO-892, first published on August 28, 2003 as PCT international publication WO03/070722, reference included with PTO-892)

Sommermeyer et al. discloses conjugates of oxidized substituted or unsubstituted starch radicals with drugs. (column 2 lines 19-51) This conjugation extends the half-life of the drug in serum by preventing passage across the kidney

barrier. (column 2 lines 55-60) Preferred starches are hydroxyethyl starches, particularly those prepared from waxy starch including waxy maize. (column 3 lines 1-8) The preferred degree of substitution is 0.1-0.8. (column 3 lines 37-40) The preferred C_2/C_6 ratio is between 3 and 11. (column 4 lines 1-5) The preferred molecular weight is between 2000-1000000 Da. (column 4 lines 39-44) These hydroxyethyl starches are preferably prepared by the method of EP0402724. (column 3 lines 51-55) The active substance to which the starch is conjugated contains an -SH group and is preferably a peptide, protein, antibiotic, nucleic acid, or hormone. (column 5 lines 9-58) The composition can be prepared as a drug containing standard pharmaceutical accessory agents. (column 7 lines 55-60) Sommermeyer et al. does not specifically disclose starches having the exact molecular weight, degree of substitution, and C_2/C_6 ratio recited in the instant claims.

It would have been obvious to one of ordinary skill in the art at the time of the invention to prepare the conjugates and compositions of Sommermeyer et al. having the molecular weight, degree of substitution, and C_2/C_6 ratio recited in the instant claims. The claimed ranges overlap or fall within the ranges disclosed in the prior art. One of ordinary skill in the art would have been able to arrive at the claimed ranges through a process of optimizing these result-effective variables within the broad disclosure of the prior art.

Therefore the invention taken as a whole is *prima facie* obvious.

Claims 62-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sommermeyer et al. as applied to claims 1, 24-34, 42, 43, 52, 60, and 61 above, and further in view of US patent 5218108. (Cited in PTO-892, herein referred to as '108)

The disclosure of Sommermeyer et al. is discussed above. Sommermeyer et al. does not disclose a process of making the claimed starch comprising the steps of claims 62-64 and 66-69.

'108 discloses a method of hydroxyehtylating starch comprising suspending a starch in water at 30% suspension with a hydroxyethylating agent and 1N sodium hydroxide, hydrolyzing the hydroxyethylated starch with acid, and purification by filtration and ultrafiltration. (column 4 lines 21-39) Note that a 30% suspension of starch in water will contain about 1.85M of glucose units. Therefore 1N of NaOH is clearly a ratio of alkalizing agent to starch of 0.54, which is greater than 0.2, if the ratio is taken to mean the ratio of alkalizing agent to glucose subunit. If the ratio is interpreted as being of alkalizing agent to entire starch molecule, the ratio would be even higher and would clearly be greater than 0.2 as well. It is also noted that '108 claims priority to foreign application DE3919729 which is the same as the publication EP0402724 cited by Sommermeyer as teaching a method of making hydroxyethyl starch suitable for use in the disclosed invention and included with Applicant's form PTO-1449.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the process of '182 to make a hydroxyethyl starch for use in the invention of Sommermeyer et al. One of ordinary skill in the art would have been motivated to make this starch because Sommermeyer et al. renders obvious a starch

having the claimed properties as discussed above. One of ordinary skill in the art would have reasonably expected success because Sommermeyer et al. specifically refers to the priority application of '182 as teaching a method of making the disclosed starches.

Regarding the sterilization step recited in instant claim 65, one of ordinary skill in the art would have been motivated to sterilize the hydroxyethyl starch because Sommermeyer et al. discloses that the conjugates are to be used as a drug. Sterilizing a pharmaceutical composition to render it suitable for therapeutic use is routine and predictable in the prior art.

Therefore the invention taken as a whole is *prima facie* obvious.

Claims 35, 37-39, 41, 45-47, 49-51, 53, 55-57, and 79-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sommermeyer et al. as applied to claims 1, 24-34, 42, 43, 52, 60, and 61 above, and further in view of Lederman et al. (US patent 6610294, cited in PTO-892)

The disclosure of Sommermeyer et al. is discussed above. Sommermeyer et al. does not disclose a composition or kit comprising a sterile aqueous solution of hydroxyethylstarch, a salt including sodium chloride, and a buffered solution.

Lederman et al. discloses a monoclonal antibody. (column 3 lines 20-39) Lederman et al. also discloses a pharmaceutical composition comprising a monoclonal antibody and a pharmaceutically acceptable carrier, including phosphate buffered saline, including sterile solutions. (column 10 lines 22-34)

It would have been obvious to one of ordinary skill in the art at the time of the invention to prepare the antibodies of Lederman et al. as starch conjugates as described by Sommermeyer et al. and to include these conjugates in a sterile solution of phosphate buffered saline. Note that phosphate buffered saline contains a salt (sodium chloride) which is also reasonably considered to be a plasma adapted electrolyte, as well as a buffer. One of ordinary skill in the art would have been motivated to do so because Sommermeyer et al. discloses that the disclosed hydroxyethyl starches can be conjugated to antibodies to improve their therapeutic properties. One of ordinary skill in the art would reasonably have expected success because preparing a pharmaceutical composition of a known active ingredient is well known and routine in the art.

Regarding a kit as claimed in claims 79-87, given that it is obvious to administer to a patient a solution of the aforementioned conjugate in sterile phosphate buffered saline, one of ordinary skill in the art would have been motivated to provide the two components in a kit. Doing so would have been routine and well within the ordinary level of skill in the art.

With regard to the mention of specific techniques such as sterile filtration and heat sterilization in claims 41 and 49, these limitation merely recite a product-by-process limitation wherein the product is required to be a product that could be prepared by the recited methods. Therefore any conventional sterilization method known by one of ordinary skill in the art would be reasonably considered to result in an equivalent sterile solution.

Therefore the invention taken as a whole is *prima facie* obvious.

Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sommermeyer et al. in view of Lederman et al. as applied to claims 35, 37-39, 41, 45-47, 49-51, 53, 55-57, and 79-87 above, and further in view of Haisma. (US patent 4775638, cited in PTO-892)

The disclosure of Sommermeyer et al. in view of Lederman et al. is discussed above. Sommermeyer et al. in view of Lederman et al. does not disclose a method comprising a step of sterile filtration or heat sterilization.

Haisma discloses a method of radiolabeling protein. (column 1 lines 45-52) In the final step, the resulting protein can be sterile filtered. (column 2 lines 50-64)

It would have been obvious to one of ordinary skill in the art at the time of the invention to sterile filter the hydroxyethyl starch used in the method of Sommermyer et al in view of Lederman. One of ordinary skill in the art would have been motivated to do so because Lederman et al. discloses that the pharmaceutical composition should be administered as a sterile solution. One of ordinary skill in the art would reasonably have expected success because Haisma discloses that sterile filtration can be used for sterilizing macromolecules such as proteins.

Therefore the invention taken as a whole is *prima facie* obvious.

Conclusion

Claims 1, 24-39, 41-47, 49-57, and 59-87 are rejected. Claims 40, 48, and 58 are objected to for depending from a rejected base claim but would be allowable if

rewritten in independent form incorporating all the limitations of the rejected base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. OLSON whose telephone number is (571)272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
10/12/2009